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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/759,777	01/12/2001	Maria Isabel Gonzalez	5771-P1-01-BD	9663

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Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/759,777	GONZALEZ ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,14 and 16-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10, 14, 16-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7-6-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed May 19, 2004 have been entered.

Claims 1,4-10, 14, 16-46 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-10, 14, and 16-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for bombesin antagonists listed in pages 8-35 in the instant specification, does not reasonably provide enablement for other bombesin antagonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that define a suitable sexual dysfunction treating "bombesin antagonists". Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "bombesin antagonists" examples are set forth. It is noted that these examples are neither exhaustive, nor define the class of compounds required since there is no structural, physical or chemical structures associated with them. The only common properties among them are their capabilities of blocking or antagonizing bombesin receptors. In other words, the claims are drawn to a method of treating sexual dysfunction by employing potentially any compounds known to men. Because of the lack of guidance to identify which compound is suitable to be used in the instant invention, the skilled artisan would be required to perform undue experimentation to screen for suitable candidate in order to ascertain suitable bombesin antagonist compounds. The employment of bombesin receptor antagonists in treating sexual dysfunction is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "bombesin antagonist(s)", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention.

Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

Response to the arguments with regard to rejection under 35 USC 112, first paragraph

Applicant's rebuttal arguments filed May 19, 2004 averring not all Wand's factors being considered, but are not found persuasive. All Wand's factors have been considered. However, MPEP clearly states that not all factors are necessarily discussed each factor in the written enablement rejection (See MPEP 2164.04). When considering the factors and the evidence as a whole, the instant claims are failed to meet the requirements set forth in 35 USC 112, first paragraph.

Applicant's rebuttal arguments filed May 19, 2004 averring the applicant not required to disclose every species encompassed by the claims have been considered, but are not found persuasive. It is true that the applicants are not required to disclose every species encompassed by their claims; however, in the instant case, the claims merely recite the use of "bombesin receptor antagonists" without disclosing what they are. Applicants, in essence, claim the method of treating sexual dysfunction by employing "any compounds that have antagonistic activity on bombesin receptor" without disclosing them what they are. By reciting the compounds as such, applicants constructively employing functional language at point of novelty. Attention is directed to *General Electric Company v. Wabash Appliance Corporation et al* 37 USPQ 466 (US 1938), at 469, speaking to functional language at the point of novelty as herein employed: "the vice of a

functional claim exists not only when a claims is "wholly" functional, if that is ever true, but when the inventor is painstaking when he recites what has already been seen, and then uses conveniently functional language at the exact point of novelty". Functional language at the point of novelty, as herein employed by Applicants, is further admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997) at 1406: stating this usage does "little more than outlin[e] goals appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". Applicants functional language at the point of novelty fails to meet the requirements set forth under 35 USC 112, first paragraph. Claims employing functional language at the point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limits of the monopoly asserted" *General Electric Company v. Wabash Appliance Corporation et* supra, at 468. Claims thus constructed provide no guidance as to medicaments employed, levels for providing therapeutic benefit, or provide notice for those practicing in the art, limits of protection. Simply stated, the presented claims are an invitation to experiment, not reciting a specific medicament regimen useful for practicing the instant invention.

Applicant's rebuttal arguments filed May 19, 2004, page 10-11, averring sufficient guidance being provided by the instant specification have been considered, but are not found persuasive. The arguments are directed to the disclosure of the instant specification with regard to how to screen candidate compounds and measure the compounds' bombesin antagonistic activities to

determine whether they are useful in the instant claims or not. However, the issue at hand is not merely how to screen a candidate compounds, but what the candidate compounds are. Without providing sufficient guidance as to chemical, structural, or physical characteristic of the bombesin receptor antagonists, any compounds known to man are a potential candidate compounds for use in the instant invention. Therefore, one of skilled in the art would have to perform undue experimentation to ascertain operable embodiments.

Applicant's rebuttal arguments filed May 19, 2004, page 12 averring large numbers of bombesin antagonists of various structures being known have been considered, but are not found persuasive. The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (See MPEP 2164.08). The large number of bombesin antagonists disclosed in the specification is considered enabled. However, it is not known what other bombesin antagonists would be useful in the herein claimed method of treating sexual dysfunction.

Applicant's rebuttal arguments filed May 19, 2004, page 12 averring other US Patents with claims to the therapeutic use of cGMP PDE inhibitors have been considered, but are not found persuasive. Examiner notes that patents are properties and not legal precedence. Every patent applications are examined on their own merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-10, 14, and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (WO 98/07718), WO96/28214, and Hurel

et al. in view of Merck Manual and sildenefil prescribing information, references of record.

Howell et al. (WO 98/07718) teaches a method of treating and/or preventing depression employing a oral pharmaceutical composition/dosage form comprising non-peptide bombesin receptor antagonists (see particularly, abstract, page 10 and claims 11-12).

WO96/28214 teaches bombesin inhibits smooth muscle contraction, splanchria vasodilation and bombesin antagonist negates these bombesin-induced biological effects (See page 5, lines 18-38).

Hurel et al. teaches that bombesin-like peptide antagonists have vasoactive properties (see page 1243).

The primary references taken together do not particularly teach the employment of bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction. Neither do they teach the combination of vasodilators, neurotransmitter antagonists and/or agonists or a horrmone like compound in its method of treating sexual dysfunction.

Merck Manual teaches depression, low testosterone level and vascular abnormalities as causes of sexual dysfunction (see pages 1575 and1577-78).

Sildenafil is a known PDE5 inhibitor vasodilator employed in the treatment of sexual dysfunction (see pages 5-6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction. It would also have been

obvious to combine the bombesin receptor antagonist with vasodilators, neurotransmitter antagonists and/or agonists or a hormone like compound in a method of treating sexual dysfunction.

One of ordinary skill in the art would have been motivated to employ bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction because (1) they are known to be employed in methods of treating depression which is known to be an underlying cause of sexual dysfunction; (2) they are known to be vasoactive which are known to be useful in treating sexual dysfunction. One of ordinary skill in the art would have also been motivated to combine the bombesin receptor antagonist with vasodilators, neurotransmitter antagonists and/or agonists or a hormone like compound in a method of treating sexual dysfunction since they are all known to be useful in treating sexual dysfunction. Combining agents that are known to be useful for the same purpose in a combination composition to be used for the same purpose is known to be within the skill of the artisan and therefore obvious, see *In re Kerkhoven* 205 USPQ 1069.

Claims 24-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (WO 98/07718), WO96/28214, and Hurel et al. in view of Merck Manual and sildenefil prescribing information, references of record as applied to claims 1, 4-10, 14, and 16-23 above, and further in view of Leiblum (International Journal of Impotence Research, 1998; 10(Suppl 2): S104-S106),

Levin (Exp. Clin. Endocrinol., 1991;98(2):61-69), Gioco et al. (US Patent 5,565,466).

Leiblum teaches different sexual disorders are affected by either mood disorder such as depression, which would reduce the desire of sexual activities, or vascular factors such as decreased vaginal lubrication which can cause pain during intercourse and female sexual arousal disorder (see particularly page S105, col. 1, second paragraph – col. 2 and page S106, col. 1).

Levin teaches VIP can increase the vaginal lubrication and induce arousal in female patients (see particularly the abstract).

Gioco et al. teaches a method of modulating the excitory phase of male and female sexual response using vasodilating agents such as phentolamine, yohimbine, α-adrenergic vasodilator, and imipramine (See col. 12, line 11 to col. 13, line 31, 45,a nd 66, Examples 3 and 4; also particularly claims 14 and 17).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the herein secondary agents with bombesin antagonist in a method of treating sexual dysfunction.

One of ordinary skill in the art would have been motivated to combine the herein secondary agents with bombesin antagonist in a method of treating sexual dysfunction because various sexual dysfunction are known to be affected by various factors such as depression and vascular. Combining the herein claimed secondary agents, which are known to correct and treat the underlying conditions that negatively affect sexual activities individually, with bombesin antagonist into

a single composition for the very same purpose would be obvious (see *In re Kerkhoven* 205 USPQ 1069), absent evidence to the contrary.

Response to the arguments with regard to rejection under 35 USC 103(a)

Applicant's rebuttal arguments filed May 19, 2004, pages 16-18 averring "obvious to try" have been considered, but are not found persuasive. The rejection is not based on "obvious to try" standard, which does not have the reasonable expectation of success. The cited prior art clearly teaches depression is one of the etiologies of sexual dysfunction. Employing bombesin antagonists to treat depression and sexual dysfunction thereby in patients that suffered sexual dysfunction secondary to depression would be reasonably expected to be effective.

Applicant's rebuttal arguments filed May 19, 2004, pages 18-19 averring that antidepressants could cause sexual dysfunction have been considered, but are not found persuasive. Applicants further argue, by citing Merck Manual, that antidepressants causes hypoactive sexual desire disorder (See Merck Manual page 1557). Examiner notes that one of ordinary skill in the art would recognize not all antidepressants causing sexual dysfunction. Te brief passage in page 1557 does not stated what mechanism of action or how antidepressants cause sexual dysfunction. Attention is directed to Merck Manual, 17th edition, pages 1533 and 1534, especially page 1533, col. 1, last paragraph, that teaches the stimulation of 5HT2 receptors produces sexual dysfunction. However, in page 1533, col. 2, Nefazodone section, teaches that nefazodone does not cause

sexual dysfunction. Moreover, mirtazapine does not cause sexual dysfunction. These two drugs do not cause sexual dysfunction because they do not have the same mechanism of action as the SSRIs do (i.e., they do not interact with the same nerochemical pathwayas the SSRIs do). As discussed in the previous office action, the antidepressant that are causing sexual dysfunction are through a specific neurological pathway, e.g., serotonin reuptake inhibitors usually cause sexual dysfunction. However, there is no reason or teachings of record to provide the reason that bombesin receptor antagonist will cause sexual dysfunction in the same way as some of the antidepressants do. Teaching away has to be clear. There is no clear teaching away present in the references of record.

Applicant's rebuttal arguments filed May 19, 2004 in page 20, averring bombesin antagonists also raising serotonin levels and "it could be assumed by one of skill in the art that such bombesin antagonists could also have anti-depressant activity" have been considered, but are not found persuasive. Examiner is not able locate the exact teachings in WO98/07718 that teaches bombesin antagonists also raise serotonin levels. Assuming the passage is true, it is still not clear what serotonin receptors the bombesin antagonists interact. As discussed above, only the stimulation of 5HT2 receptors produces sexual dysfunction. Without evidence to the contrary, possessing the teachings of the cited prior arts, one of ordinary skill in the art would have been motivated to employ bombesin antagonists as taught in the cited prior arts in a method of treating sexual dysfunction.

Applicant's rebuttal arguments filed May 19, 2004 in pages 20-21, averring WO96/28214 nor Hurel not teaching or suggesting bombesin antagonists as useful to treat sexual dysfunction. Examiner notes that if viewing WO96/28214 alone, one of ordinary skill in the art may not find motivation to employ bombesin antagonists to treat sexual dysfunction. However, when viewing the teachings of the cited prior arts as a whole, it is clear that bombesin antagonists are useful in vasodilatation as evidenced that bombesin antagonists are smooth muscle contraction inhibitor (i.e., vasoconstriction inhibitors) and are useful in treating hypertension. A vasocontriciton promoter would not be expected to have a hypotensive effect. Therefore, when taking the prior arts as a whole, one of ordinary skill in the art would have been motivated to employ the bombesin antagonists taught in the cited prior arts to treat sexual dysfunction.

Applicant's rebuttal arguments filed May 19, 2004 in pages 21-22 averring Hurel et al. not providing suggestions to believe bombesin antagonists as vasodilators have been considered, but are not found persuasive. Applicants specially argue that the systemic blood pressure was increased after the infusion of bombesin antagonist (See Table in Hurel). Examiner notes that in the control (placebo), the blood pressure is actually fluctuated as evidenced by the fact that the SD is 21. Therefore, the systemic pressure is from 152 ± 21 mmHg (i.e., 131-173 mmHg). The recorded blood pressure for bombesin antagonist group is 166 mmHg, which is well within the wide range of blood pressure recorded for the control (placebo). Thus, it is clear that the blood pressure alone is not a good measure to determine whether bombesin antagonist as a vasodilator or not.

Rather, when one of ordinary skill in the art look at the data presented in Hurel, one would see that the systemic vascular resistance is clearly decreased from 21.48 to 21.08. Taken with the teachings of Howell et al. and WO96/28214, one of ordinary skill in the art would be reasonable expected bombesin antagonist as vasodilators. As discussed in the rejections, one of ordinary skill in the art would have been motivated to employ bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction because (1) they are known to be employed in methods of treating depression which is known to be an underlying cause of sexual dysfunction; (2) they are known to be vasoactive which are known to be useful in treating sexual dysfunction.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is

(571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Patent Examiner
Art Unit 1617